The Invention

The invention is directed, *inter alia*, to a controlled release dosage form of azithromycin, as defined in terms of *in vitro* criteria. The dosage form can operate by sustained release, as claimed in claims 72 and 125, or by delayed release, as claimed in claim 96. The claims are limited to azithromycin as the antibiotic.

Claims 72-76, 80-86, 93-129, 133-139, and 146-148 stand rejected under 35 USC §103 over Curatolo et al., further in view of Handsfield et al, Lee and Robinson. The reference to "Lee and Robinson" in the general statement of the rejection (page 4, first three lines of paragraph 1), is not understood as Applicants were unable to locate the names "Lee" or "Robinson" on any of the references, and they were not discussed further in the body of the Office Action. On the other hand, although Urquhart (US 4,851,231) and Edgren (US 4,522,625) were not specifically mentioned in the general statement of the rejection, Applicants have treated the rejection as though Urquhart and Edgren were intended as secondary references, particularly as they are discussed in the body of the rejection and listed on the "Notice of References Cited" (PTO-892) which the Examiner appended to the Office Action.

The rejection is traversed on the basis that, absent Applicants' specification, there is no basis for combining the references in the manner of the rejection, and that the rejection is otherwise based on hindsight which is universally recognized as impermissible.

First, the Examiner has based the rejection on a total of four different references (Curatolo, Handsfield, Urquhart, and Edgren), but such a combination of references is improper unless the prior art suggests the combination, which is not the case here. See In re Bond, 15 Uspq2d 1566 (Fed. Cir. 1990) in which it was held that the PTO erred in rejecting a claimed invention as an obvious combination of the teachings of two prior art references when the prior art provided no teaching, suggestion, or incentive supporting the combination. See also Smithkline Diagnostics v. Helena Laboratories Corp., 8 USPQ2d 1468, where the court stated that a challenger to the validity of a patent "cannot pick and choose among the individual teachings of assorted prior art references to recreate the claimed invention"; the challenger has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination. See also In re Mahurkar Patent Litigation, 28 USPQ2d 1801 (N.D. Ill. 1993) where it was

stated that decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming it is easy to reassemble these elements into the invention is a forbidden *ex post* analysis.

> An invention lies in a combination of elements that are themselves mundane.....Unless the prior art itself suggests the particular combination, it does not show that the actual invention was obvious or anticipated. [28 USPQ2d at 1817]

In the instant Office Action, it is not seen how a rejection to a claimed controlled release dosage form of azithromycin can be based on Curatolo 5,505,889, the primary reference, which teaches immediate release and, accordingly, teaches away from controlled release. That is, Curatolo claim 1 (see also claims 4 and 9) requires that the claimed dosage forms therein effect dissolution of at least 90% of their contained azithromycin within 30 minutes when tested by the method and under the conditions also disclosed therein. The claim clearly requires an azithromycin dosage form to effect immediate and/or fast release of its contained azithromycin, i.e., 90% within 30 minutes. Because of its express fast/immediate release requirements one skilled in the art of controlled release dosage forms would undoubtedly dismiss Curatolo out of hand as simply unrelated to controlled release, and would certainly not consider it as being relevant to the instant invention.

Further, the instant claims are limited to azithromycin as the antibiotic. There was no reason *ab initio* to expect that putting azithromycin in a controlled release form would be of benefit. This is true especially when one considers that, as known in the art, the half life of azithromycin is 69 hours, meaning that it stays around in the body for a comparatively long time. The dosage forms of this invention either meter azithromycin out or delay its release over a period of several hours. When an antibiotic has a half life of 69 hours, which is long compared with "several hours", the scale for release in the instant claims, how can it be obvious that putting azithromycin in a controlled release dosage form will be of therapeutic benefit? Since azithromycin stays in the body a long time, one would normally expect that controlled release over several hours would be no different than administering azithromycin in an immediate release form since, either way, the azithromycin persists in the body for a long time, certainly longer than the time scale for release in the instant invention.

The instant inventors, by conducting intubation studies as demonstrated in the Examples, determined that the side effects of azithromycin are mediated in the upper

gastrointestinal (GI) tract. That is why controlled release azithromycin ameliorates side effects even though azithromycin has a long half life. The azithromycin is metered out slowly or delayed until the bulk of the drug has passed the upper GI tract. Until the inventors conducted their studies, the origin or reason for azithromycin's side effects were unknown, however. There is no prior art known to the inventors that identifies the origin or cause of azithromycin side effects, or that discloses that the side effects are locally mediated, rather than systemically mediated. Not until the local nature of the side effects was determined by the inventors did it make sense to think about putting azithromycin in a controlled release dosage form.

Because none of the prior art cited by the Examiner suggests that the side effects of azithromycin are locally mediated, and further fails to suggest a controlled release dosage form of azithromycin otherwise, the only way one of ordinary skill in the art would find it obvious to make a controlled release dosage form of azithromycin is through the impermissible use of hindsight, in effect using that which only the inventors have taught against them.

Further, the secondary references do not otherwise fill in the gaps left by Curatolo. None of them makes any suggestion to put azithromycin in a controlled release dosage form. In this respect, Edgren and Urquhart are simply examples of controlled release dosage forms, but with no suggestion to put azithromycin in a controlled release dosage form. Handsfield simply demonstrates that azithromycin is a good, effective antibiotic.

Thus it is Applicants position that the only way one of ordinary skill in the art would combine the cited references is by using hindsight which, as discussed above, may not be used as the basis for a rejection. It is respectfully submitted that, without knowledge of Applicants' intubation studies and/or a suggestion in the prior art to formulate azithromycin in a controlled release dosage form, Applicants invention does not even rise to the level of "obvious to try". Even allowing, for the sake of argument only, that the invention were misconstrued as being "obvious to try", however, the law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success,** viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied 502 U.S. 856 (1991). In the present case, it is respectfully submitted that the prior art contains no such suggestion. Moreover there is no "expectation of success" provided that any benefit would accrue. Thus it is respectfully submitted that the references do not make the claimed invention obvious. Withdrawal of the rejection is accordingly courteously solicited.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

DATE: Dec. 3, 2001

James T. Jones
Agent for the Applicants
Reg. No. 30,561

Pfizer Inc.
Patent Dept.
Eastern Point Road
Groton, CT. 06340
(860)441-4903